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Effect of lowering postprandial hyperglycemia on insulin secretion in older people with impaired glucose tolerance

Annette M. Chang,[1] Marla J. Smith,[1] Cathie J. Bloem,[1] Andrzej T. Galecki,[2] and Jeffrey B. Halter[1,2]

[1]*Department of Internal Medicine, University of Michigan, Ann Arbor 49109;*
and [2]*Institute of Gerontology, University of Michigan, Ann Arbor, Michigan 48109*

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Chang, Annette M., Marla J. Smith, Cathie J. Bloem, Andrzej T. Galecki, and Jeffrey B. Halter. Effect of lowering postprandial hyperglycemia on insulin secretion in older people with impaired glucose tolerance. *Am J Physiol Endocrinol Metab* 287: E906–E911, 2004. First published June 22, 2004; doi:10.1152/ajpendo.00156.2004.—Glucose tolerance declines with age, resulting in a high prevalence of diabetes and impaired glucose tolerance (IGT) in the older population. Hyperglycemia per se can lead to impaired β-cell function (glucose toxicity). We tested the role of glucose toxicity in age-related β-cell dysfunction in older people (65 ± 8 yr) with IGT treated with the α-glucosidase inhibitor acarbose (n = 14) or placebo (n = 13) for 6 wk in a randomized, double-blind study. Baseline and posttreatment studies included *1*) an oral glucose tolerance test (OGTT), *2*) 1-h postprandial glucose monitoring, *3*) a frequently sampled intravenous glucose tolerance test (insulin sensitivity, or S_I), and 4) glucose ramp clamp (insulin secretion rates, or ISR), in which a variable glucose infusion increases plasma glucose from 5 to 10 mM. The treatment groups had similar baseline body mass index; fasting, 2-h OGTT, and 1-h postprandial glucose levels; and S_I. In these carefully matched older people with IGT, both fasting (5.7 ± 0.2 vs. 6.3 ± 0.2 mM, P = 0.002) and 1-h postprandial glucose levels (6.9 ± 0.3 vs. 8.2 ± 0.4 mM, P = 0.02) were significantly lower in the acarbose than in the placebo group. Despite this reduction of chronic hyperglycemia in the acarbose vs. placebo group, measures of insulin secretion (ISR area under the curve: 728 ± 55 vs. 835 ± 81 pmol/kg, P = 0.9) and acute insulin response to intravenous glucose (329 ± 67 vs. 301 ± 54 pM, P = 0.4) remained unchanged and impaired. Thus short-term improvement of chronic hyperglycemia does not reverse β-cell dysfunction in older people with IGT.

β-cell function; glucose intolerance; aged humans

THE PREVALENCE OF TYPE 2 DIABETES and impaired glucose tolerance (IGT) increases with age (6). More than 25% of the older population meets current diagnostic criteria for type 2 diabetes (15, 24). An additional 20% of this population meets criteria for IGT, defined as a 2-h glucose level ≥7.8 mM but <11.1 mM by oral glucose tolerance testing (OGTT) and a fasting glucose <7.0 mM (15). Isolated postchallenge hyperglycemia, defined as a 2-h glucose level ≥11.1 mM by OGTT, but a fasting glucose level <7.0 mM, is particularly common in people over age 60 (1, 10, 11, 29).

IGT, as with type 2 diabetes, is characterized by both insulin resistance (13, 20) and defects in β-cell function (13, 20, 30). Multiple risk factors for type 2 diabetes associated with aging may predispose older people to develop glucose intolerance and increased insulin resistance. Insulin secretory defects have been consistently demonstrated even with normal aging, with greater defects in older people with IGT (2, 6, 8). Over time, chronic exposure to hyperglycemia in older people with IGT may cause a further decline in β-cell function. Studies in animal models and humans suggest that chronic hyperglycemia may have adverse effects on insulin secretion, an effect called glucose toxicity (25).

α-Glucosidase inhibitors, such as acarbose, act by inhibiting enzymes in the small intestine, thereby decreasing glucose absorption and improving postprandial hyperglycemia. In the STOP-NIDDM (non-insulin-dependent diabetes mellitus) diabetes prevention trial, acarbose treatment decreased the progression to diabetes in people with IGT by 25% compared with placebo (9). Acarbose has also been found to normalize postprandial hyperglycemia and to improve insulin sensitivity in a study of eight obese middle-aged people with IGT (10). It was thought that insulin sensitivity might have improved at least in part through a decrease in glucose toxicity, because α-glucosidase inhibitors do not have direct effects on insulin secretion or sensitivity.

The effect of a reduction in chronic hyperglycemia on impaired insulin secretion in older people with postchallenge hyperglycemia has not been previously examined. In the present study, we investigated the role of chronic postprandial hyperglycemia in age-related β-cell dysfunction. Older people with postchallenge hyperglycemia were treated with an α-glucosidase inhibitor, acarbose, or placebo for 6 wk in a randomized, double-blind study.

MATERIALS AND METHODS

Participants

The protocol was approved by the University of Michigan Institutional Review Board and performed in accordance with the Declaration of Helsinki. After the nature of the study was explained in detail, informed consent was obtained from all participants. Healthy, community-dwelling older people were recruited by advertisement to participate in a study of glucose metabolism and aging. A total of 30 older men and women, age ≥50 yr, were recruited, of whom 27 (9 men, 18 women) completed the protocol. Health status and glucose tolerance were assessed by screening medical history, physical examination, blood chemistries (liver enzymes, creatinine, electrolytes, and glucose), complete blood count, electrocardiogram, and a 75-g OGTT. Subjects with postchallenge hyperglycemia were enrolled. For the purposes of this study, postchallenge hyperglycemia was defined as fasting plasma glucose <7.0 mM and 2-h plasma glucose ≥7.8 mM and ≤13.9 during the OGTT.

Address for reprint requests and other correspondence: J. B. Halter, Univ. of Michigan, 1111 CCGC Bldg., 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0926 (E-mail: jhalter@umich.edu).

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Study Design

The study was double blind, randomized, and placebo controlled. Subjects were randomized to treatment with either acarbose or placebo for a 6-wk dosing period. To minimize the known gastrointestinal side effects of acarbose, the study medication and matching placebo were started at a dose of 25 mg/day and gradually titrated to 100 mg three times per day. All participants met with the dietician before randomization and were instructed on a weight-maintenance diet for the duration of the 6-wk dosing period. The nurse study coordinator was in weekly contact with the participants to review side effects, medication compliance, and weight-maintenance diet.

Study Protocols.

Measurement of insulin sensitivity and β-cell function was performed on two occasions: at baseline before acarbose/placebo treatment and upon completion of the dosing period. The studies were performed on 2 consecutive days and after overnight fasts. The insulin-assisted frequently sampled intravenous glucose tolerance test (FSIGT) was performed on one day, followed by the ramp clamp protocol on the second day. Study medication was withheld on the morning of posttreatment studies. A 75-g OGTT and 1-h postprandial glucose measurements were used to assess the effect of treatment on the degree of reduction of hyperglycemia. One-hour postprandial home glucose monitoring was performed for 3 days, or 9 total meals, before randomization to study medication and at completion of the dosing period. Participants used the Elite XL glucometer and consumed their standard weight-maintenance diet. Hemoglobin A_{1c} and safety laboratory tests (liver function tests, creatinine, and complete blood counts) were measured at the screening visit and at completion of the dosing period.

FSIGT. On *day 1*, the insulin-assisted FSIGT was performed as described by Bergman et al. (3), with the addition of insulin to enhance precision of the estimates of insulin action (31). Subjects reported after an overnight (12-h) fast. An intravenous catheter was placed in each arm for insulin and glucose infusions and blood sampling. At *time 0*, 50% dextrose (0.3 g/kg) was injected intravenously over 30 s, followed by injection of insulin (0.02 U/kg) over 30 s at 20 min. Twenty-eight blood samples were collected periodically over the 180 min after the glucose bolus.

The sensitivity to insulin index (S_I) was calculated from a least squares fitting of the temporal pattern of glucose and insulin throughout the FSIGT by use of the minimal model of glucose kinetics (3). The acute insulin response to intravenous glucose (AIRg) was calculated as the mean rise in plasma insulin above baseline at 3, 4, and 5 min after intravenous glucose administration. To assess insulin secretion independent of changes in insulin sensitivity, the product of AIRg and S_I, or the disposition index, was also calculated as previously described (4, 19).

Glucose ramp clamp. On *day 2*, the glucose ramp protocol was initiated after an overnight fast, as previously described (7). The aim of this procedure was to assess insulin secretion in response to gradually increasing plasma glucose levels from ~5 to 10 mM over 3 h. An antecubital intravenous catheter was placed for insulin and glucose infusions. A second intravenous catheter was inserted in a dorsal hand/wrist vein of the contralateral arm and placed into a warming box heated to 60°C to obtain arterialized blood samples for glucose and insulin. After an initial baseline sample was taken, a small intravenous dose of insulin (0.007–0.014 units/kg) was administered to lower the glucose level to ~5 mM. After the insulin had been allowed to decay (20 min after bolus insulin), an intravenous infusion of 20% dextrose was started. Samples were drawn every 10 min for determination of insulin, C-peptide, and glucose. For each of the 10-min samples, plasma glucose was measured using a Beckman glucose analyzer, and the glucose infusion rate was adjusted to achieve a linear increase of plasma glucose levels from 5 to 10 mM over 3 h, closely matching glucose levels in all subjects.

The ISR during the ramp clamp protocol was derived by deconvolution of peripheral C-peptide concentrations and by previously determined C-peptide kinetics (28). The total ISR over the 40- to 220-min time interval was estimated for each subject by calculating the area under the curve with the trapezoidal rule (ISR AUC). As described above, ISR AUC was also multiplied by S_I to determine the disposition index.

Assays

Plasma glucose levels during the ramp clamp protocol were measured at the bedside by the glucose oxidase technique with an interassay coefficient of variation (CV) of 3.0% (Beckman, Palo Alto, CA). Hemoglobin A_{1c} was measured by HPLC with a normal range of 3.8–6.4%. All other blood samples were centrifuged, and serum was stored at −20°C until analysis by the Chemistry Laboratory of the Michigan Diabetes Research and Training Center. Plasma glucose levels during the FSIGT studies were measured using a hexokinase method with an interassay CV of 3.1% (Roche Diagnostics, Indianapolis, IN). Plasma insulin was quantified using a highly specific and sensitive double-antibody radioimmunoassay with an interassay CV of 3.4% and an intra-assay variability of 2.5% (Linco Research). Plasma C-peptide was measured by double-antibody radioimmunoassay with interassay and intra-assay CVs of 9.4 and 2.5%, respectively (Linco Research). Fasting plasma free fatty acid (FFA) concentrations were measured by an original, enzymatic, colorimetric assay with an interassay CV of 4.7% and an intra-assay variability of 3.6% (Wako Chemicals, Richmond, VA).

Statistical Analysis

Data are presented as means ± SE, with the exception of subject characteristics, which are presented as means ± SD. The primary objective was to compare the effects of acarbose vs. placebo on β-cell responsiveness to hyperglycemia as assessed by ISR AUC during the glucose ramp clamp studies. The secondary objectives were to compare *1*) the effects of acarbose vs. placebo on S_I derived from the FISGT to account for the possible effect of S_I to modulate insulin secretion, *2*) the effects of acarbose vs. placebo on fasting glucose, and *3*) the effects of acarbose vs. placebo on 1-h postprandial glucose.

The effect of acarbose vs. placebo treatment on ISR AUC was analyzed with a multiple regression model corresponding to an analysis of covariance to control for baseline levels of ISR AUC. Similar multiple regression analyses were performed to assess the effect of acarbose vs. placebo treatment on S_I, fasting glucose, and 1-h postprandial glucose, with control for baseline levels of these measurements. Two-sided tests were performed with a $P = 0.05$ level of significance.

RESULTS

Enrollment

The first older participant with postchallenge hyperglycemia was enrolled in February 2002 and the last in December 2003. The study was completed in January 2004. Of the 30 participants who enrolled, 3 dropped out of the study. Two subjects assigned to placebo dropped out, one due to an inability to obtain intravenous access (before randomization to study medication) and the other due to gastrointestinal symptoms after randomization. One subject assigned to acarbose withdrew due to gastrointestinal side effects. Analyses were performed for the 13 placebo and 14 acarbose-treated subjects who completed the protocol.

Baseline Participant Characteristics

As shown in Table 1, the acarbose- and placebo-treated older people with postchallenge hyperglycemia were well

Table 1. *Characteristics of study subjects*

	Placebo	Acarbose
n	13	14
Age, yr	64±9	66±8
Gender (male/female)	4/9	5/9
Weight, kg	92±19	86±11
BMI, kg/m^2	32±5	33±4
Waist circumference, cm	109±13	104±12
OGTT glucose, mM		
Fasting	6.1±0.5	6.2±0.6
2-h	9.8±1.6	10.3±1.2
Hemoglobin A_{1c}, %	5.7±0.5	5.6±0.4

Data are means ± SD. BMI, body mass index; OGTT, oral glucose tolerance test.

matched. Baseline weight, body mass index (BMI), waist circumference, and fasting and 2-h OGTT glucose levels were not significantly different in the two treatment groups.

Effects of Treatment

Baseline and posttreatment measures of glucose tolerance, insulin secretion, and insulin sensitivity are summarized in Table 2. There were no statistically significant differences in baseline fasting or 1-h postprandial glucose levels, fasting insulin, or S_I between the acarbose and placebo groups. As shown in Table 2, acarbose treatment resulted in significantly lower fasting glucose levels compared with placebo treatment (5.7 ± 0.2 vs. 6.3 ± 0.2 mM, $P = 0.002$) in a multiple regression model after controlling for baseline fasting glucose. There was also a significant difference in the change in (Δ)fasting glucose with acarbose compared with placebo treatment (−0.48 ± 0.14 vs. +0.21 ± 0.13, $P = 0.001$).

As displayed in Table 2, acarbose treatment resulted in significant reductions in 1-h postprandial glucose levels compared with placebo treatment (6.9 ± 0.3 vs. 8.2 ± 0.4 mM, $P = 0.02$) in a multiple regression model after controlling for baseline 1-h postprandial glucose. There was also a significant difference in the Δ1-h postprandial glucose with acarbose compared with placebo treatment (−0.22 ± 0.28 vs. +0.86 ± 0.33, $P = 0.001$).

As shown in Table 2, fasting insulin levels were not significantly different posttreatment in the acarbose compared with placebo group (105 ± 16 vs. 140 ± 21 pM, $P = 0.2$). In addition, S_I was not significantly altered with acarbose or placebo treatment (1.1 ± 0.1 vs. 1.0 ± 0.1 $10^{-5}\cdot min^{-1}\cdot pM^{-1}$, $P = 0.4$). As detailed in Table 2, there was a trend toward higher fasting FFA levels at baseline in the acarbose compared with the placebo group ($P = 0.09$). However, posttreatment levels were not significantly different between the two groups ($P = 0.9$) in a multiple regression model after controlling for baseline levels. In addition, weight, BMI, and waist circumference remained unchanged in the two groups posttreatment.

The primary measure of insulin secretion in the study was provided with the glucose ramp clamp. As shown in Fig. 1, *A* and *C*, glucose levels during the ramp clamp procedures were well matched in the fasting state and throughout the studies. Total glucose infused during the ramp clamp protocols to achieve this comparable glucose stimulus was unchanged with acarbose compared with placebo treatment (175 ± 11 vs. 172 ± 15 ml, $P = 0.8$).

As shown in Fig. 1, *B* and *D*, ISR increased in response to increasing glucose concentrations in both treatment groups during the ramp studies. The placebo group had somewhat higher baseline and posttreatment ISR during the ramp clamp studies compared with the acarbose group. Average ISR did not change significantly compared with baseline in either treatment group. As displayed in Table 2, β-cell sensitivity to glucose as assessed by ISR AUC was unchanged with acarbose compared with placebo treatment (728 ± 55 vs. 835 ± 81 pmol/kg; $P = 0.9$) in a multiple regression model after controlling for baseline ISR AUC. An additional measure of insulin secretion, AIRg during FISGT studies, remained unchanged with acarbose compared with placebo treatment (332 ± 67 vs. 275 ± 55 pM, $P = 0.4$).

Adjustment of insulin secretion for changes in insulin sensitivity, or the disposition index (ISR AUC or AIRg × S_I), was not significantly different with acarbose compared with placebo treatment (ISR AUC × S_I: 718 ± 58 vs. 710 ± 93 pmol/kg × $10^{-5}\cdot min^{-1}\cdot pM^{-1}$, $P = 0.3$; AIRg × S_I:

Table 2. *Summary measures*

	Placebo		Acarbose	
	Baseline	6 wk	Baseline	6 wk
BMI, kg/m^2	31.9±1.3	31.9±1.3	32.6±1.2	32.7±1.2
Waist, cm	109.5±3.5	111.5±3.7	103.6±3.3	104.9±2.9
OGTT				
Fasting glucose, mM	6.1±0.1	6.3±0.2	6.2±0.2	5.7±0.2†
2-h Glucose, mM	9.8±0.4	9.8±1.0	10.3±0.4	9.8±0.9
Fasting insulin, pM	126±25	140±21	102±12	105±16
1-h Postprandial glucose, mM	7.3±0.3	8.2±0.4	7.2±0.3	6.9±0.3*
Fasting free fatty acid, meq/l	0.9±0.1	0.8±0.1	1.3±0.2	1.0±0.1
FSIGT				
S_I, $10^{-5}\cdot min^{-1}\cdot pM^{-1}$	1.2±0.2	1.0±0.1	1.1±0.1	1.1±0.1
AIRg, pM	299±71	301±54	310±67	329±67
AIRg × S_I, pM × $10^{-5}\cdot min^{-1}\cdot pM^{-1}$	249±77	259±49	280±63	324±78
Ramp clamp				
ISR AUC, pmol/kg	848±84	835±81	725±55	728±55
ISR AUC × S_I, pmol/kg × $10^{-5}\cdot min^{-1}\cdot pM^{-1}$	971±188	710±93	759±87	718±58

Data are means ± SE. FSIGT, frequently sampled in glucose tolerance test; S_I, insulin sensitivity; AIRg, acute insulin response to in glucose; ISR AUC, insulin secretion rate area under the curve. *$P = 0.02$, †$P = 0.002$, acarbose vs. placebo posttreatment groups by multiple regression.

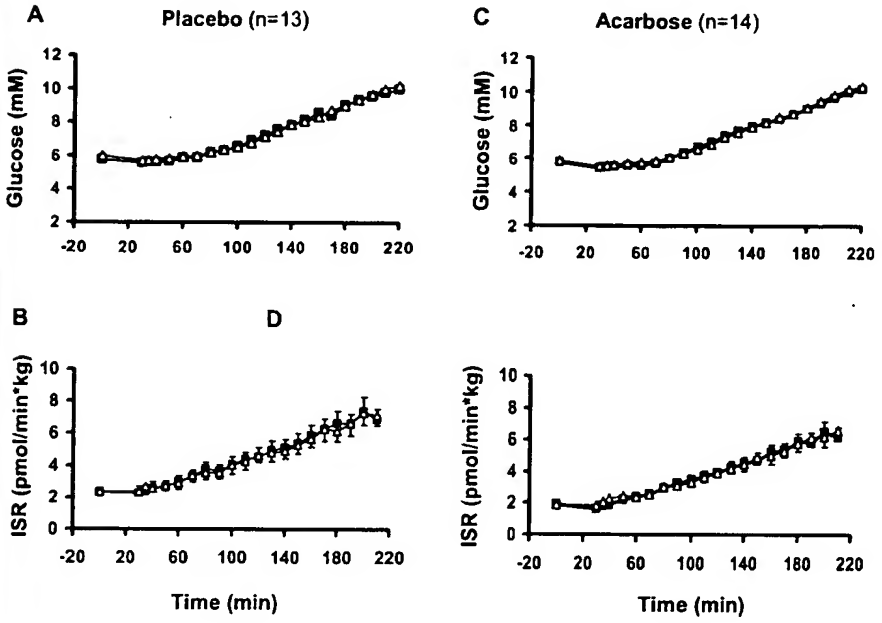

Fig. 1. Profiles of plasma glucose concentrations and insulin secretion rate (ISR) over time during the glucose ramp clamp studies. Glucose (*A*) and ISR (*B*) vs. time before (■) and after (△) treatment with placebo (*left*) in older subjects with postchallenge hyperglycemia. Glucose (*C*) and ISR (*D*) vs. time before (■) and after (△) treatment with acarbose (*right*) in older subjects with postchallenge hyperglycemia. Glucose levels during variable-rate glucose infusion begun at *time 0* were well matched before and after treatment in the acarbose and placebo groups. Average ISR did not change from baseline in either treatment group. ISR was derived by deconvolution of peripheral C-peptide concentrations. Data are means + SE.

324 ± 78 vs. 260 ± 49 pM × 10^{-5}·min^{-1}·pM^{-1}, $P = 0.3$) in multiple regression models with control for baseline measurements.

DISCUSSION

Chronic hyperglycemia itself has been shown to have adverse effects on both insulin secretion and insulin action, a concept called glucose toxicity (25). Animal models have shown that chronic hyperglycemia impairs the ability of the pancreas to respond to an acute glucose stimulus, and correction of hyperglycemia completely reverses β-cell dysfunction (25). Thus it is conceivable that postchallenge hyperglycemia, although modest, could contribute to impaired pancreatic β-cell function in age-related glucose intolerance.

The effect of a reduction in chronic hyperglycemia on impaired insulin secretion in older people with postchallenge hyperglycemia has not been previously examined. In this study, we investigated the possibility that age-related β-cell dysfunction may be secondary to chronic hyperglycemia. Six weeks of α-glucosidase inhibitor treatment resulted in significant reductions in both fasting and 1-h postprandial glucose levels compared with placebo treatment. Despite this short-term reduction in hyperglycemia, measures of insulin secretion remained unchanged and impaired compared with previously studied younger and older people with normal glucose tolerance (7, 8). These results differ from studies in younger people with type 2 diabetes that showed improved insulin secretion with as little as 20 h to 10 days of improved glycemic control (16, 27), although these studies included people with overt hyperglycemia.

Other studies have examined the effect of α-glucosidase inhibitors on insulin secretion in people with type 2 diabetes with findings of no change in insulin release in elderly people with well-controlled diabetes (21) as well as decreased (14), unchanged (23), or increased (17) insulin levels in response to mixed meals. In our study involving older people with postchallenge hyperglycemia, insulin sensitivity also remained unchanged with acarbose treatment. This is in contrast to a pilot study by Chiasson et al. (10) in which acarbose improved insulin sensitivity in middle-aged people with IGT. The effects of acarbose on insulin sensitivity in people with type 2 diabetes are also conflicting, with findings of both improved (5, 21) and unchanged insulin sensitivity (18, 23, 26).

The participants in our study on average had S_I values per FSIGT indicative of severe insulin resistance. In light of the previously described hyperbolic relationship between β-cell function and insulin sensitivity (19), perhaps our subjects were already maximally compensated for their level of insulin re-

sistance and were not able to increase insulin secretion even after a decline in hyperglycemia.

A limitation of this study is the 6-wk intervention with acarbose or placebo. Despite this limited treatment period, α-glucosidase inhibitor treatment resulted in significant improvements in fasting and postprandial hyperglycemia. However, we cannot exclude the possibility that longer-term reduction of hyperglycemia would result in improved insulin secretion in this population.

Glucose toxicity itself cannot be measured, and it is unknown whether the degree of hyperglycemia in our subjects with predominantly postprandial hyperglycemia and mildly elevated fasting glucose levels in the range of impaired fasting glucose is sufficient to cause hyperglycemia-mediated impairment of insulin secretion. However, in healthy young people with normal glucose tolerance, 12-h infusion of high-dose glucose to achieve hyperglycemia in the range seen in people with IGT has been shown to impair insulin secretion (22). Recent studies have suggested that even mild hyperglycemia may be associated with impaired insulin secretion in humans. In lean people with normal glucose tolerance, a progressive decline in β-cell function was identified in people with 2-h OGTT glucose levels >5.6 mM compared with those with glucose levels <5.6 mM (12).

In summary, α-glucosidase inhibitor treatment of older adults with postchallenge hyperglycemia resulted in significant improvements in both fasting and postprandial hyperglycemia compared with placebo treatment. Despite this reduction in mild, chronic hyperglycemia, measures of insulin secretion remained unchanged and impaired compared with previously studied older and younger people with normal glucose tolerance. In conclusion, short-term improvement of chronic hyperglycemia does not reverse insulin secretory dysfunction in older people with postchallenge hyperglycemia. Future work will be crucial to further characterize age-related glucose intolerance and β-cell dysfunction to develop effective prevention and treatment strategies in this population at high risk for diabetes and its complications.

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